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(54) **Title:** TOPICAL TREATMENT OF STREPTOCOCCAL INFECTIONS

(57) **Abstract:** The present invention discloses a method and composition for the topical treatment of streptococcal infections by the use of a lysin enzyme blended with a carrier suitable for topical application to dermal tissues. The method for the treatment of dermatological streptococcal infections comprises administering a composition comprising effective amount of a therapeutic agent, with the therapeutic agent comprising a lysin enzyme produced by group C streptococcal bacteria infected with a C1 bacteriophage. The therapeutic agent can be in a pharmaceutically acceptable carrier.

What is claimed is:

1) A method for the treatment of dermatological streptococcal infections comprising:

administering to an infected area of the body a composition comprising effective amount of a therapeutic agent, said therapeutic agent comprising a lysin enzyme produced by group C streptococcal bacteria infected with a C1 bacteriophage.

2) The method according to claim 1, further comprising delivering said therapeutic agent in a pharmaceutically acceptable carrier.

3) The method according to claim 2, wherein said carrier is selected from the group consisting of an aqueous liquid, an alcohol base, a water soluble gel, a lotion, an ointment, a nonaqueous liquid base, a mineral oil base, a blend of mineral oil and petrolatum, lanolin, liposomes, hydrophilic gelling agents, cross-linked acrylic acid polymers (carbomers), cellulose polymers, hydroxy ethyl cellulose, cellulose gum, MVE/MA decadiene crosspolymers, PVM/MA copolymers, and any combinations thereof.

4) The method according to claim 1, wherein the form in which the composition is delivered is selected from the group consisting of a spray, a smear, a time release patch, a liquid absorbed wipe, and any combinations thereof.

5) The method according to claim 1, wherein the lysin enzyme is in an environment having a pH which allows for activity of said lysin enzyme.

6) The method according to claim 5, wherein said composition further comprises a buffer that maintains pH of the composition at a range between about 4.0 and about 9.0.

7) The method according to claim 6, wherein said buffer maintains the pH of the composition at the range of between about 5.5 and about 7.5.

8) The method according to claim 6, wherein said buffer comprises a reducing agent.

9) The method according to claim 8, wherein said reducing agent is dithiothreitol.

10 The method according to claim 6, wherein said buffer comprises a metal chelating reagent.

11) The method according to claim 10, wherein said metal chelating reagent is ethylenediaminetetraacetic disodium salt.

12) The method according to claim 6, wherein said buffer is a citrate-phosphate buffer.

13) The method according to claim 6, further comprising a bactericidal or bacteriostatic agent as a preservative.

14) The method according to claim 1, wherein the therapeutic agent further comprises a mild surfactant in an amount effective to potentiate the therapeutic effect of the lysin enzyme.

15) The method according to claim 1, wherein the therapeutic agent further comprises at least one complementary agent which potentiates the bactericidal activity of the lysine enzyme, said complementary agent being selected from the group consisting of penicillin, synthetic penicillins bacitracin, methicillin, cephalosporin, polymyxin, cefaclor. Cefadroxil,

cefamandole nafate, cefazolin, cefixime, cefmetazole, cefonioid, cefoperazone, ceforanide, cefotanme, cefotaxime, cefotetan, cefoxitin, cefpodoxime proxetil, ceftazidime, ceftizoxime, ceftriaxone, cefriaxone moxalactam , cefuroxime, cephalexin, cephalosporin C, cephalosporin C sodium salt, cephalothin, cephalothin sodium salt, cephapirin, cephradine, cefuroximeaxetil, dihydratecephalothin, moxalactam, loracarbef. mafate and chelating agents in an amount effective to synergistically enhance the therapeutic effect of the lysin enzyme.

16) The method according to claim 1, wherein the therapeutic agent further comprises lysostaphin for the treatment of any *Staphylococcus aureus* bacteria.

17) The method according to claim 1, wherein the therapeutic agent further comprises mutanolysin.

18) The method according to claim 1, wherein the therapeutic agent further comprises lysozyme.

19) The method according to claim 1, wherein said lysin enzyme is present in an amount ranging from about 100 to about 500,000 units per milliliter.

20). The method according to claim 19, wherein said lysin enzyme is present in an amount ranging from about 1,000 units to about 100,000 units per milliliter.

21) The method according to claim 20, wherein said lysin enzyme is present in an amount ranging from about 10,000 units to about 100,000 units per milliliter.

22) A composition for the treatment of dermatological streptococcal infections comprising:

an effective amount of a therapeutic agent, said therapeutic agent comprising a lysin enzyme produced by group C streptococcal bacteria infected with a C1 bacteriophage, and a pharmaceutically acceptable carrier for topical application of the lysin enzyme.

23) The composition according to claim 22, wherein said carrier is selected from the group consisting of an aqueous liquid, an alcohol base, a water soluble gel, a lotion, an ointment, a nonaqueous liquid base, a mineral oil base, a blend of mineral oil and petrolatum, lanolin, liposomes,
hydrophilic gelling agents, cross-linked acrylic acid polymers (carbomers), cellulose polymers, hydroxy ethyl cellulose, cellulose gum, MVE/MA decadiene crosspolymers, PVM/MA copolymers, and any combinations thereof.

24) The composition according to claim 22, wherein said composition is in the form selected from the group consisting of a spray, a smear, a time release patch, a liquid absorbed wipe, and any combinations thereof.

25) The composition according to claim 22, wherein the lysin enzyme is in an environment having a pH which allows for activity of said lysin enzyme.

26) The composition according to claim 20, wherein said composition further comprises a buffer that maintains pH of the composition at a range between about 4.0 and about 9.0.

27) The composition according to claim 26, wherein said buffer maintains the pH of the composition at the range of between about 5.5 and about 7.5.

28) The composition according to claim 26, wherein said buffer comprises a reducing agent.

29) The composition according to claim 28, wherein said reducing agent is dithiothreitol.

30) The composition according to claim 26, wherein said buffer comprises a metal chelating reagent.

31) The composition according to claim 30, wherein said metal chelating reagent is ethylenediaminetetraacetic disodium salt.

32) The composition according to claim 26, wherein said buffer is a citrate-phosphate buffer.

33) The composition according to claim 22, further comprising a bactericidal or bacteriostatic agent as a preservative.

34) The composition according to claim 22, further comprising a surfactant in an amount effective to potentiate the therapeutic effect of the therapeutic agent.

35) The composition according to claim 22, wherein the therapeutic agent further comprises at least one complementary agent which potentiates the bactericidal activity of the lysine enzyme, said complementary agent being selected from the group consisting of penicillin, synthetic penicillins bacitracin, methicillin, cephalosporin, polymyxin, cefaclor. Cefadroxil, cefamandole nafate, cefazolin, cefixime, cefmetazole, cefonioid, cefoperazone,

ceforanide, cefotanme, cefotaxime, cefotetan, cefoxitin, cefpodoxime proxetil, ceftazidime, ceftizoxime, ceftriaxone, cefriaxone moxalactam , cefuroxime, cephalexin, cephalosporin C, cephalosporin C sodium salt, cephalothin, cephalothin sodium salt, cephapirin, cephradine, cefuroximeaxetil, dihydratecephalothin, moxalactam, loracarbef. mafate chelating agents, and combinations thereof in an amount effective to synergistically enhance the therapeutic effect of the lysin enzyme.

36) The composition according to claim 22, wherein the therapeutic agent further comprises lysostaphin for the treatment of any *Staphylococcus aureus* bacteria.

37) The composition according to claim 22, wherein the therapeutic agent further comprises
mutanolysin.

38) The composition according to claim 22, wherein the therapeutic agent further comprises
lysozyme.

39) The composition according to claim 22, wherein said lysin enzyme is present in an amount ranging from about 100 to about500,000 units per milliliter.

40). The composition according to claim 22, wherein said lysin enzyme is present in an amount ranging from about 1,000 units to about 100,000 units per milliliter.

41) The composition according to claim 22, wherein said lysin enzyme is present in an amount ranging from about 10,000 units to about 100,000 units per milliliter.

42) The composition according to claim 22, further comprising at least one emulsifier.

43) The composition according to claim 22, further comprising at least one antioxidant.

44) The composition according to claim 22, further comprising at least one sunscreen.

45) The composition according to claim 22, further comprising at least one preservative.

46) The composition according to claim 22, further comprising at least one anti-inflammatory agent.

47) The composition according to claim 22, further comprising at least one local anesthetic.

48) The composition according to claim 22, further comprising at least corticosteroid.

49) The composition according to claim 22, further comprising at least one destructive therapy agent.

INTERNATIONAL SEARCH REPORT

Interi ...al Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/48 A61P31/04 A61K9/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X, L	US 5 997 862 A (FISCHETTI ET AL.) 7 December 1999 (1999-12-07) the priority claim of the present application might not be partially justified. the whole document	22-32, 43,45
Y	US 5 604 109 A (FISCHETTI ET AL.) 18 February 1997 (1997-02-18) cited in the application claim 19	1-7,19, 39
Y	FR 2 357 246 A (MARTINEZ) 3 February 1978 (1978-02-03) the whole document	1-7,19, 39

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 9838 Derwent Publications Ltd., London, GB; AN 1988-444917 XP002141110 & RU 2 103 991 C (IMMUNOPREPARAT RES PRODN ASSOC), 10 February 1998 (1998-02-10) abstract ---	22,23, 25,26
X	DATABASE WPI Week 9715 Derwent Publications Ltd., London, GB; AN 1997-163380 XP002141111 & RU 2 064 299 C (AS USSR MICROORGANISMS BIOCHEM PHYSIOLOG ET AL.) abstract ---	22,23, 25,26
A	US 4 062 941 A (DAVIES) 13 December 1977 (1977-12-13) the whole document -----	

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5997862 A	07-12-1999	US 6017528 A	25-01-2000
		US 5985271 A	16-11-1999
		US 6056954 A	02-05-2000
US 5604109 A	18-02-1997	AU 8108587 A	06-05-1988
		CA 1301645 A	26-05-1992
		EP 0285649 A	12-10-1988
		JP 1501338 T	11-05-1989
		JP 2837846 B	16-12-1998
		WO 8802781 A	21-04-1988
FR 2357246 A	03-02-1978	NONE	
RU 2103991 C		NONE	
RU 2064299 C	27-07-1996	NONE	
US 4062941 A	13-12-1977	GB 1542848 A	28-03-1979